International Searching Authority
European Patent Office
Erhardtstraße 27
D-80298 München
GERMANY

31 October 2005

Sent by fax

Dear Sirs

PCT Patent Application No PCT/GB2004/005100
IMPERIAL COLLEGE INNOVATIONS LIMITED
Our Ref; ICOBW/P32126PC

This is a response to the written opinion of the International Searching Authority. Please note that we are not requesting international preliminary examination.

Turning to the numbered items in the written opinion:

III

1. We note the examiner's comments and will attend to this objection at the national phase.

2. Claim 27 has been deleted.

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3. We disagree with the examiner that Claims 17 to 19 lack novelty. While it may be true that D1 *mentions* that a T cell line has been made which is able to recognise the peptide RMFPNAPYL, the particular T cell line (line 77) was not made available to the public by the publication of D1 for two reasons.

   Firstly, the T cell line 77 was not distributed to anyone prior to the filing date of the application and, furthermore, as far as we are aware there was no obligation on any of the authors to do so.

   Secondly, there is not sufficient information in D1 to be able to produce

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the host cells of Claims 17 to 19 which requires the presence of the polynucleotide of any of Claim 12 to 14 or the expression vector of Claims 15 or 16, which the examiner has already accepted are novel and inventive.

New Claim 18 requires the presence of an *expression vector* which expresses at least the alpha chain or beta chain of the TCR and so is novel for the additional reason that the T cell line 77 in D1 does not contain an expression vector that encodes either the alpha or beta chains of the particular TCR.

Thus, new Claims 17 to 20 are undoubtedly novel.

4.1 Since the T cell line mentioned in D1 was not made available to the public before the filing date of the application (as discussed above), the examiner's argument in relation to old Claims 20 to 24 fails.

It also fails because these claims specifically relate to a *modified* T cell, which is modified to express the particular TCR molecule as set out in Claims 1 to 11. The examiner has already accepted that Claims 1 to 11 are novel and inventive. Their use (as in old Claims 20 to 24) must also be novel and inventive.

New Claims 23 and 27 require the presence of an expression vector which expresses at least the alpha or beta chain of the TCR, and the examiner has already acknowledged that such expression vectors are novel and inventive.

4.2 Claim 1 has been amended to indicate that the TCR molecule is one which is able to bind to an HLA-A2/RFMPNAPYL complex. A basis for this amendment is found, for example, on page 7, lines 2 and 3.

It is conventional practice at the EPO to define variation in biological molecules in this sort of way, and we note that the patent specification provides adequate details for the skilled person to obtain the molecules as defined. We also note that it is CDR3 which is primarily involved in peptide recognition, while CDR1 and CDR2 are more involved with HLA interaction and are therefore less critical with respect to the specificity of the TCR molecule for the peptide.

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The invention as claimed certainly does solve the problem and has an inventive step.

A reasonable degree of substitution is appropriate in order to give the applicant a fair degree of protection bearing in mind the very significant contribution to the art that has been made. Furthermore, the scope of the claim is commensurate with the contribution to the art made by the inventors.

Yours faithfully
ERIC POTTER CLARKSON

John S Miles PhD hs

Enc: Replacement pages 20-23

CLAIMS

1. A T cell receptor (TCR) molecule containing an alpha chain portion and a beta chain portion wherein the alpha chain portion contains three complementarity determining regions (CDRs):
CDR1α: SSYSPS
CDR2α: YTSAATL
CDR3α: VVSPFSGGGADGLT or comprising or consisting of SPFSGGGADGLT
and the beta chain portion contains three complementarity determining regions (CDRs):
CDR1β: DFQATT
CDR2β: SNEGSKA
CDR3β: comprising SARDGGEG or comprising or consisting of RDGGEGSETQY, or wherein up to three amino acid residues in one or more of the CDRs are replaced by another amino acid residue, which TCR molecule is able to bind to an HLA-A2/RFMPNAPYL complex.

2. A TCR molecule according to Claim 1 wherein CDR3α has the amino acid sequence VVSPFSGGGADGLT.

3. A TCR molecule according to Claim 1 wherein the CDR3α has the amino acid sequence SPFSGGGADGLT.

4. A TCR molecule according to Claim 1 wherein the CDR3β has the amino acid sequence SARDGGEG.

5. A TCR molecule according to Claim 1 wherein the CDR3β has the amino acid sequence RDGGEGSETQY.

6. A TCR molecule according to any one of the preceding claims wherein the alpha chain portion and the beta chain portion are present on different

polypeptide chains.

7. A TCR molecule according to any one of Claims 1 to 5 wherein the alpha chain portion and the beta chain portion are present in the same polypeptide chain.

8. A TCR molecule according to any of Claims 1 to 7 wherein the CDRs are grafted to a human framework region.

9. A TCR molecule according to Claim 8 wherein the alpha chain portion has the amino acid sequence given in Figure 2.

10. A TCR molecule according to Claims 8 or 9 wherein the beta chain portion has the amino acid sequence given in Figure 4.

11. A TCR molecule according to any one of Claims 1 to 10 which is soluble.

12. A polynucleotide encoding the alpha chain portion as defined in Claim 1.

13. A polynucleotide encoding the beta chain portion as defined in Claim 1.

14. A polynucleotide encoding the single chain TCR molecule as defined in Claim 7.

15. An expression vector comprising a polynucleotide according to any of Claims 12 to 15.

16. An expression vector according to Claim 15 which is a retroviral vector.

17. A host cell comprising a polynucleotide according to any of Claims 12 to 14 or an expression vector according to Claims 15 or 16.

18. A host cell comprising an expression vector according to Claims 15 or 16.

19. A host cell according to Claim 17 or 18 which is a T cell.

20. A host cell according to Claim 19 which is a T cell derived from a patient.

21. A method of combating a WT1-expressing malignancy in a patient, the method comprising introducing into the patient a T cell, preferably derived from the patient, which is modified to express the TCR molecule of any of Claims 1 to 11.

22. A method according to Claim 21 comprising (1) obtaining T cells from the patient, (2) introducing into the T cells a polynucleotide according to any of Claims 12 to 14 or an expression vector according to Claims 15 or 16 so that the T cell expresses the encoded TCR molecule and (3) introducing the cells from step (2) into the patient.

23. A method according to Claim 22 wherein an expression vector is used in step (2).

24. A method according to Claim 21 or 22 wherein the WT1-malignancy is any one or more of breast cancer, colon cancer, lung cancer, leukaemia, ovarian cancer, melanoma, head and neck cancer, thyroid cancer, glioblastoma and sarcoma.

25. Use of a T cell, preferably a patient derived T cell, modified to express the TCR molecule of any of Claims 1 to 11 in the manufacture of a medicament for combating a WT1-expressing malignancy in the patient.

26. Use according to Claim 25 wherein a polynucleotide according to any of Claims 12 to 14 or an expression vector according to Claims 15 or 16 has been introduced into the T cell, preferably patient derived T cell, so that

the T cell expresses the encoded TCR molecule.

27. Use according to Claim 26 wherein an expression vector has been introduced into the T cell.

28. A method of selecting a TCR molecule with improved binding to an HLA-A2/RMFPNAPYL complex comprising (a) providing a TCR molecule containing an alpha chain portion and a beta chain portion wherein the alpha chain portion contains three complementarity determining regions (CDRs):
CDR1α: SSYSPS
CDR2α: YTSAATL
CDR3α: VVSPFSGGGADGLT or comprising or consisting of SPFSGGGADGLT
and the beta chain portion contains three complementarity determining regions (CDRs):
CDR1β: DFQATT
CDR2β: SNEGSKA
CDR3β: comprising SARDGGEG or comprising or consisting of RDGGEGSETQY.

wherein at least one amino acid residue in one or more of the CDRs as given is replaced with another amino acid residue, (b) determining whether the TCR molecule binds to an HLA-A2/RFMPNAPYL complex with greater affinity than a TCR molecule without the replacement amino acid(s), and (c) selecting a molecule which binds with greater affinity.

29. A method according to Claim 28 wherein the CDR3s are as defined in any of Claims 2 to 9.